



Therapeutic Class Review Non-Benzodiazepine Anxiolytics

I. Overview

This class review includes non-benzodiazepine medications that are used primarily for the relief of anxiety disorders. There are 4 agents in this class and they differ in their structures, mechanisms of action, and pharmacologic profiles.

Anxiety states are a collection of conditions in which a generalized pervasive fear dominates a patient's life. Anxiety disorders include the following: generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress, and social phobias.¹

The miscellaneous anxiolytics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Buspirone, hydroxyzine and meprobamate are available in at least one generic dosage form.

Table 1. Non-benzodiazepine Anxiolytics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
buspirone	tablet	Buspar [®]
hydroxyzine hydrochloride	injection, syrup, tablet	(previously Atarax [®])
hydroxyzine pamoate	capsule	Vistaril [®]
meprobamate	tablet	(previously Miltown [®])

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the non-benzodiazepine anxiolytics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Non-benzodiazepine Anxiolytics

Clinical Guideline	Recommendation(s)
International Consensus Group on Depression and Anxiety: Consensus Statement on Panic Disorder (1998) ⁵	<p><u>General Considerations</u></p> <ul style="list-style-type: none"> The goal of treatment is full remission across the syndrome: panic attacks, anxiety, phobias, well-being, and disability. The strongest evidence for clinical efficacy exists for selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and benzodiazepines. Monoamine oxidase inhibitors (MAOIs) have demonstrated efficacy, though the quality of evidence is less extensive. There is limited evidence for the use of anticonvulsants, and recommended use of valproate is confined to treatment-resistant patients. β-Blockers should be considered an ineffective therapeutic option in panic disorder. <p><u>Treatment of Choice</u></p> <ul style="list-style-type: none"> SSRIs are recommended as first-line treatment of panic disorder. SSRI treatment is to be initiated at a low dose and increased slowly, as tolerated, to

	<p>the target dose.</p> <ul style="list-style-type: none"> • Effective treatment may be continued for 12 to 24 months with consideration for stopping only when the patient is well and in a stable life situation, after which treatment may be discontinued slowly over the course of 4 to 6 months; treatment should never be stopped abruptly. • Concomitant use of a benzodiazepine for a limited period (<8 weeks) may be used to help initiate treatment with an SSRI in some patients. <p><u>Second-line Treatment</u></p> <ul style="list-style-type: none"> • Second-line treatment is needed when a patient fails to respond to an adequate trial (8 to 12 weeks) of an SSRI at the maximum tolerated dose. • If partial response was observed and the SSRI was well tolerated, switch to another SSRI. • If an SSRI was not tolerated, initiate a trial of a benzodiazepine or a TCA. <p><u>Third-line Treatment</u></p> <ul style="list-style-type: none"> • An MAOI or valproate may be tried. <p><u>Additional Pertinent Considerations</u></p> <ul style="list-style-type: none"> • SSRIs are generally preferable to benzodiazepines or TCAs based on a review of long-term treatment data. • SSRIs may be administered in a once-daily dosing regimen (except fluvoxamine); clomipramine may be given as a single dose at bedtime; however, other TCAs require multiple dosing as do benzodiazepines. • Patients with panic disorder and a recent history of alcoholism should, except in some instances, not be prescribed benzodiazepines. • Patients who have panic disorder and a history of suicidal ideation or temporal lobe epilepsy should not be prescribed TCAs. • SSRIs are an appropriate choice of treatment for patients with panic disorders who also have concomitant depression, high suicidality, or concomitant medical illness. • SSRIs should be the preferred therapeutic option for panic disorder comorbid with other anxiety disorders (eg, obsessive-compulsive disorder) or alcoholism. • Benzodiazepines are generally well tolerated but may cause unwanted sedative effects, poor coordination, and memory problems; may potentiate the effects of alcohol; and are associated with the risk of dependence with long-term use as well as potential difficulties with withdrawal symptoms. • TCAs are associated with poor tolerability due to their anticholinergic effects, may cause weight gain, and have the potential to cause seizures as well as other safety concerns. • SSRIs have an improved tolerability over traditional TCAs and most side effects resolve over time; some SSRIs may cause initial jitteriness.
<p>International Consensus Group on Depression and Anxiety: Consensus Statement on Generalized Anxiety Disorder (GAD) (2001)⁶</p>	<p><u>General Considerations</u></p> <ul style="list-style-type: none"> • Chronic worrying and the effects of chronic tension are the specific features that define GAD; duration of symptoms is an important factor differentiating GAD from other anxiety disorders. For a diagnosis of GAD, the symptoms of anxiety and worry should have been present for 6 months. • Cognitive behavioral therapy (CBT) techniques are recommended as the preferred form of psychotherapy in GAD. • When GAD is comorbid with depression, as it commonly is, medication is often indicated. <p><u>Treatment of Choice</u></p> <ul style="list-style-type: none"> • Antidepressants are recommended as first-line treatment of GAD. The following classes of antidepressants can be used:

	<ul style="list-style-type: none"> ○ Selective serotonin-reuptake inhibitors (SSRIs) ○ Serotonin-norepinephrine reuptake inhibitors (SNRIs) ○ Nonsedating tricyclic antidepressants (TCAs) <ul style="list-style-type: none"> • Benzodiazepines may be used as adjunct agents in acute exacerbations of GAD or for sleep disturbances during the initiation of antidepressant therapy. Patients should be stabilized on antidepressant therapy for >4 weeks before benzodiazepines are slowly tapered off (over 4 to 8 weeks). • For patients with a long-term condition, with several comorbid conditions, and in patients with an increased risk of suicide, an SSRI or SNRI is indicated. <p><u>Other Therapeutic Options</u></p> <ul style="list-style-type: none"> • Buspirone has demonstrated efficacy in GAD in most clinical trials, although it has not shown efficacy against comorbid conditions and therefore is not recommended as first-line treatment for GAD. <p><u>Additional Pertinent Considerations</u></p> <ul style="list-style-type: none"> • The guideline indicates that the only first-line use of benzodiazepines is an acute anxiety reaction, with an expected duration of 2 to 6 weeks; benzodiazepines are not appropriate for first-line treatment of GAD, which is a condition requiring appropriate long-term treatment. • Benzodiazepines are appropriate for intermittent or episodic use. • Benzodiazepines may have a role as adjunctive therapy in acute exacerbation of GAD or in sleep disturbances during the initiation of antidepressant therapy. • GAD is frequently comorbid with depressive disorders, for which benzodiazepines are not desirable, or with other anxiety disorders, for which benzodiazepine therapy is not usually favored as first-line. • The use of benzodiazepines may be a problem in the long term, due to the risk of withdrawal reactions, or in patients with a history of drug abuse or alcoholism. • The guideline indicates that hydroxyzine is used in acute anxiety states, in which it is targeting symptoms rather than treating the condition itself. • The use of hydroxyzine is similar to that of benzodiazepines; however, hydroxyzine does not cause dependence. • Hydroxyzine has no demonstrated efficacy in depression, panic disorder, social phobia, or obsessive-compulsive disorder. • Neuroleptics are not appropriate for the treatment of GAD as there is almost no clinical evidence to support their use, and may be associated with tardive dyskinesias.
<p>National Institute for Health and Clinical Excellence (NICE): Management of Anxiety (Panic Disorder, With or Without Agoraphobia, and Generalized Anxiety Disorder) in Adults in Primary, Secondary and Community Care (2004)⁷</p>	<p><u>Panic Disorder General Considerations</u></p> <ul style="list-style-type: none"> • Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder. More effective options are outlined below. • Sedating antihistamines or antipsychotics should not be prescribed for panic disorder. <p><u>Panic Disorder Treatment Options</u></p> <p>Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:</p> <ul style="list-style-type: none"> • Psychological therapy (ie, cognitive behavioral therapy, structured problem solving, psychoeducation) • Pharmacological therapy: antidepressants • Self-help interventions (ie, bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface) <p><u>Panic Disorder Additional Considerations for Pharmacologic Therapy</u></p> <ul style="list-style-type: none"> • Antidepressants should be the only pharmacologic intervention used in the longer

	<p>term.</p> <ul style="list-style-type: none">• Two types of medication are considered in the guideline for the treatment of panic disorder; tricyclic antidepressants (TCAs) and selective serotonin-reuptake inhibitors (SSRIs).• Unless otherwise indicated, an SSRI (eg, paroxetine, fluvoxamine, citalopram) licensed in the United Kingdom (UK) for panic disorder should be offered; if an SSRI is not suitable, the TCAs imipramine or clomipramine may be considered.• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.• If the patient is showing improvement, the medication should be continued for at least 6 months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.• If there is no improvement after a 12-week course with an SSRI and if a further medication is appropriate, imipramine or clomipramine may be considered, or another form of therapy may be offered. <p><u>Generalized Anxiety Disorder General Considerations</u></p> <ul style="list-style-type: none">• Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks. <p><u>Generalized Anxiety Disorder Treatment Options</u></p> <p>Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:</p> <ul style="list-style-type: none">• Psychological therapy (eg, cognitive behavioral therapy, structured problem solving, psychoeducation)• Pharmacological therapy: antidepressants• Self-help interventions (eg, bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface) <p><u>Generalized Anxiety Disorder Additional Considerations for Pharmacologic Therapy</u></p> <ul style="list-style-type: none">• Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered.• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.• If the patient is showing improvement the medication should be continued for at least 6 months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.• If there is no improvement after a 12 week course with an SSRI and if a further medication is appropriate, another SSRI may be considered, or another form of therapy may be offered.• If venlafaxine is being considered, an initial electrocardiogram (ECG) and blood pressure measurement should be undertaken and the dose should be no higher than 75 mg per day; treatment should be initiated and managed under the supervision of specialist mental health medical practitioners and regular monitoring of cardiac status is advised.• A number of different drugs are considered for the treatment of GAD in the guideline, including SSRIs (eg, paroxetine, fluvoxamine, citalopram), TCAs (eg, imipramine, clomipramine), benzodiazepines (eg, diazepam, alprazolam, clonazepam, lorazepam), sedating antihistamines (eg, hydroxyzine), SNRIs (eg, venlafaxine), and buspirone.• Antidepressants are preferred over benzodiazepines due to the potential for abuse and
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<p>International Consensus Group on Depression and Anxiety: Consensus Statement on Social Anxiety Disorder (SAD) (1998)⁸</p>	<p>because antidepressants may treat comorbid depression.</p> <p><u>General Considerations</u></p> <ul style="list-style-type: none"> SAD appears to predispose individuals to the development of other psychiatric disorders, most notably depression. There is some evidence for the effectiveness of cognitive behavioral treatment in SAD; however, this is based on relatively small trials as compared to that for pharmacotherapy. <p><u>Treatment of Choice</u></p> <ul style="list-style-type: none"> Selective serotonin-reuptake inhibitors (SSRIs) are recommended as first-line treatment of SAD, with most efficacy evidence for SSRIs derived from well-controlled studies with paroxetine. The appropriate dosage regimen for paroxetine has been defined: it should be initiated at 20 mg/day for 2 to 4 weeks, and then increased as necessary. An adequate trial of treatment with an SSRI is 6 to 8 weeks, and if effective, treatment should be continued for at least 12 months. Long-term treatment is indicated if symptoms are unresolved, if the patient has a comorbidity or a history of relapse, or if there was an early onset of SAD. SSRIs are also recommended for treating patients who have failed to respond to other treatments for SAD. <p><u>Other Therapeutic Options</u></p> <ul style="list-style-type: none"> Phenelzine, a monoamine oxidase inhibitor (MAOI), has less evidence for efficacy in SAD and is associated with concerns about its tolerability and safety, which make it an inappropriate option for first-line treatment. The benzodiazepine clonazepam has limited but well-controlled data for the treatment of SAD; alprazolam was shown to be significantly less effective than clonazepam for SAD, and there is no evidence that benzodiazepines as a class are effective in SAD. <p><u>Additional Pertinent Considerations</u></p> <ul style="list-style-type: none"> β-Blockers do not have a place in the management of SAD; despite the benefit of their use with normal performance anxiety, there is no controlled evidence to show that β-blockers are advantageous for the pathologic anxiety of generalized SAD. Furthermore they may have harmful effects, especially in patients with asthma. In contrast with their efficacy in panic disorder, there are no controlled data for the efficacy of tricyclic antidepressants (TCAs) in SAD. There is no evidence for the efficacy of buspirone in SAD.
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III. Indications

Food and Drug Administration (FDA)-approved indications for the non-benzodiazepine anxiolytics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Non-benzodiazepine Anxiolytics^{2-4, 9-12}

Drug	Alcohol Withdrawal Syndrome	Anxiety Disorders	Anxiety Symptoms, Short-Term Relief	Anxiety Due to Drug Withdrawal	Nausea and Vomiting	Pruritus	Sedation
Buspirone		✓ *	✓ *				
Hydroxyzine hydrochloride	✓		✓ * ‡		✓ (excluding pregnancy)	✓ *	✓ § (pre- or postoperative, pre- or postpartum)
Hydroxyzine pamoate			✓ *			✓ *	✓ (premedication or following general anesthesia)
Meprobamate		✓ *	✓ *				

*Effectiveness in long-term use (more than 3 to 4 weeks for buspirone and more than 4 months for hydroxyzine hydrochloride or pamoate or meprobamate) has not been demonstrated in controlled clinical trials.

‡Agent can be used to manage the acutely disturbed or hysterical patient.

§Agent can be used pre- or postoperative, pre- or postpartum to allay anxiety, permit reduction in narcotic dosage, and control emesis.

IV. Pharmacokinetics

The pharmacokinetic parameters for the non-benzodiazepine anxiolytics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Non-benzodiazepine Anxiolytics^{2-4, 9-12}

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Buspirone	90	86	Hepatic (CYP3A4)	Yes; 1-pyrimidinyl-piperazine	Fecal (18-38), renal (29-63)	2-3
Hydroxyzine	Not reported	Not reported	Hepatic	Yes; cetirizine	Not reported	3-20
Meprobamate	Not reported	0-30	Hepatic	None	Renal (10-12 unchanged within 24 hours)	9-11

N/A=not available

V. Drug Interactions

Significant drug interactions with the non-benzodiazepine anxiolytics are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Non-benzodiazepine Anxiolytics^{3,4}

Drug(s)	Significance Level	Interaction	Mechanism
Buspirone	1	Monoamine oxidase inhibitors (isocarboxazid, pargyline, phenelzine, procarbazine, selegiline, tranlycypromine)	Concurrent administration of buspirone with monoamine oxidase inhibitors (MAOIs) is not recommended. Cases of hypertensive crisis have occurred when MAOIs have been administered simultaneously with buspirone. This interaction may be mediated by the affinity of buspirone for serotonin receptors. Allow 14 days to elapse between withdrawal of the MAOI and administration of buspirone.
Buspirone	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, miconazole)	Azole antifungals may inhibit the CYP3A4 isozyme responsible for first-pass metabolism of buspirone, resulting in elevated plasma levels and increased pharmacologic and adverse effects.
Buspirone	2	Diltiazem	Diltiazem may enhance the bioavailability of buspirone by reducing the first-pass metabolism (CYP3A4) of buspirone. The pharmacologic and adverse effects of buspirone may be increased.
Buspirone	2	Macrolide and related antibiotics (clarithromycin, erythromycin, telithromycin)	Macrolide and related antibiotics may inhibit the CYP3A4 isozyme responsible for first-pass metabolism of buspirone, resulting in elevated plasma levels and increased pharmacologic and adverse effects
Buspirone	2	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may induce first-pass metabolism (CYP3A4) of buspirone. Buspirone plasma concentrations and pharmacologic effects may be decreased.
Buspirone	2	Verapamil	Verapamil may enhance the bioavailability of buspirone by reducing the first-pass metabolism (CYP3A4) of buspirone. The pharmacologic and adverse effects of buspirone may be

Drug(s)	Significance Level	Interaction	Mechanism
			increased.
Meprobamate	2	Ethanol	Acute ethanol ingestion results in decreased clearance of drugs through inhibition of hepatic metabolic systems. With chronic ethanol ingestion, one may manifest tolerance presumably due to enhanced metabolic capacity. The combination may result in enhanced CNS depressant effects affecting coordination and judgment.

Significance Level 1=major severity

Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the non-benzodiazepine anxiolytics are noted in Table 6.

Table 6. Common Adverse Events (%) Reported with the Non-Benzodiazepine Anxiolytics^{2-4, 9-12}

Adverse Event	Buspirone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate
Cardiovascular				
Arrhythmia	-	-	-	✓
Chest pain	≥1	-	-	-
ECG changes, transient	-	-	-	✓
Hypertension	≤1	-	-	-
Hypotension (includes postural)	≤1	-	-	✓
Palpitation	1	-	-	✓
Peripheral edema	-	-	-	✓
Syncope	≤1	-	-	✓
Tachycardia	1	-	-	✓
Central Nervous System				
Akathisia	≤1	-	-	-
Anger/hostility	2	-	-	-
Ataxia	-	-	-	✓
Confusion	2	-	-	-
Convulsions	≤1	✓	✓	-
Decreased concentration	2	-	-	-
Depersonalization	≤1	-	-	-
Depression	2	-	-	-
Dissociative reaction	≤1	-	-	-
Dizziness	12	-	-	✓
Dream disturbances	≥1	-	-	-
Drowsiness	10	✓	✓	✓
Dysphoria	≤1	-	-	-
Euphoria	≤1	-	-	✓
Excitement	2	-	-	✓
Fast EEG activity	-	-	-	✓
Fatigue	4	-	-	-
Fearfulness	≤1	-	-	-
Hallucinations	≤1	-	✓	-
Headache	6	✓	✓	✓
Incoordination	1	-	-	-

Adverse Event	Buspirone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate
Insomnia	3	-	-	-
Involuntary movements	≤1	✓	✓	-
Libido decreased	≤1	-	-	-
Libido increased	≤1	-	-	-
Lightheadedness	3	-	-	-
Malaise	≤1	-	-	-
Nervousness	5	-	-	-
Numbness/ paresthesia	1-2	-	-	✓
Overstimulation	-	-	-	✓
Psychomotor retardation	≤1	-	-	-
Somnolence	10	✓	✓	✓
Speech disorder	-	-	-	✓
Suicidal ideation	≤1	-	-	-
Tremor	1	✓	✓	-
Vertigo	-	-	-	✓
Dermatological				
Dry skin	≤1	-	-	-
Ecchymosis	≤1	-	-	✓
Edema	≤1	-	-	-
Hair loss	≤1	-	-	-
Petechiae	-	-	-	✓
Pruritis	≤1	-	✓	✓
Purpura	-	-	-	✓
Rash	1	-	✓	✓
Urticaria	-	-	✓	✓
Gastrointestinal				
Abdominal pain	2	-	-	-
Anorexia/ weight loss	≤1	-	-	-
Appetite increased/ weight gain	≤1	-	-	-
Colitis	≤1	-	-	-
Constipation	1	-	-	-
Diarrhea	2	-	-	✓
Dry mouth	3	✓	✓	-
Flatulence	≤1	-	-	-
Nausea	8	-	-	✓
Salivation	≤1	-	-	-
Rectal bleeding	≤1	-	-	-
Vomiting	1	-	-	✓
Hematologic				
Agranulocytosis	-	-	-	✓
Aplastic anemia	-	-	-	✓
Eosinophilia	-	-	-	✓
Leukopenia	-	-	-	✓
Laboratory Test Abnormalities				
SGOT elevation	≤1	-	-	-
SGPT elevation	≤1	-	-	-
Musculoskeletal				
Arthralgia	≤1	-	-	-
Leg/muscle cramps	≤1	-	-	-

Adverse Event	Buspirone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate
Myalgia	1	-	-	-
Weakness	2	-	-	✓
Respiratory				
Hyperventilation	≤1	-	-	-
Pulmonary congestion	≤1	-	-	-
Shortness of breath	≤1	-	-	-
Throat sore/irritation	≥1	-	-	-
Special Senses				
Conjunctivitis	≤1	-	-	-
Dysgeusia/taste perversion	≤1	-	-	-
Eye redness/itching	≤1	-	-	-
Hyperacusis	≤1	-	-	-
Labyrinthitis	-	-	-	-
Nasal congestion	≥1	-	-	-
Parosmia	≤1	-	-	-
Tinnitus	≥1	-	-	-
Visual disturbance	2	-	-	✓
Other				
Adenopathy	-	-	-	✓
Allergic reactions	-	-	✓	✓
Cross reaction to carisoprodol	-	-	-	✓
Dysuria	≤1	-	-	-
Exacerbation of porphyric symptoms	-	-	-	✓
Fever/hyperpyrexia	≤1	-	-	✓
Menstrual irregularities	≤1	-	-	-
Sore throat	≥1	-	-	-
Sweating/clamminess	1	-	-	-
Urinary frequency/incontinence	≤1	-	-	-
Urinary hesitancy	≤1	-	-	-

-Event not reported or incidence <1%

✓ Percent not specified

ECG=electrocardiogram, EEG=electroencephalogram, ER=extended release, GGT= gamma-glutamyl transferase, HCl=hydrochloride, IR=immediate release, SGOT=serum glutamic oxaloacetic transaminase (aspartate aminotransferase), SGPT=serum glutamic pyruvic transaminase (alanine aminotransferase)

Drug Abuse and Dependence

Meprobamate is categorized as schedule C-IV by the Drug Enforcement Agency (DEA) because of its abuse potential. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. There are limited studies that have evaluated the long-term safety and efficacy of this agent.

Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence.¹⁶

VII. Dosing and Administration

The usual dosing regimens for the non-benzodiazepine anxiolytics are summarized in Table 7.

Table 7. Usual Dosing for the Non-benzodiazepine Anxiolytics^{2-4, 9-12}

Drug	DEA Schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Not a controlled substance	<u>Anxiety:</u> Initial, 15 mg daily (7.5 mg twice daily); dosage may be increased 5 mg per day every two to three days as needed; maximum daily dose: not to exceed 60 mg per day	Safety and efficacy in children <18 years have not been established.	Tablet: 5 mg 7.5 mg 10 mg 15 mg 30 mg
Hydroxyzine hydrochloride	Not a controlled substance	<u>Anxiety, Acutely Disturbed or Hysterical Patients or Alcohol Withdrawal:</u> 50-100 mg IM and every four to six hours as needed <u>Nausea and Vomiting (Excluding Pregnancy Associated):</u> 25-100 mg IM <u>Sedation, Adjunctive Medication Pre- and Postoperative and Pre- and Postpartum:</u> 25-100 mg IM	<u>Nausea and Vomiting (Excluding Pregnancy Associated):</u> 0.5 mg/lb IM <u>Sedation, Adjunctive Medication Pre- and Postoperative:</u> 0.5 mg/lb IM	Syrup: 10 mg/5 mL Tablet: 10 mg 25 mg 50 mg Vial: 25 mg/mL 50 mg/mL
Hydroxyzine pamoate	Not a controlled substance	<u>Anxiety:</u> 50-100 mg four times daily <u>Pruritis:</u> 25 mg three or four times a day <u>Sedation, Premedication or Following General Anesthesia:</u> 50-100 mg	<u>Anxiety:</u> 6 years and older: 50-100 mg daily in divided doses Under 6 years: 50 mg daily in divided doses <u>Pruritus:</u> 6 years and older: 50-100 mg daily in divided doses Under 6 years: 50 mg daily in divided doses <u>Sedation, Premedication or Following General Anesthesia:</u> 0.6 mg/kg	Capsule: 25 mg 50 mg 100 mg
Meprobamate	IV	<u>Anxiety:</u> 1,200-1,600 mg per day in three or four divided doses; maximum: 2,400 mg per day	<u>Anxiety:</u> 6-12 years: 200-600 mg per day in two or three divided doses Not recommended for children <6 years of age.	Tablet: 200 mg 400 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the non-benzodiazepine anxiolytics are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Non-benzodiazepine Anxiolytics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Anxiety				
Gammans et al ¹³ Buspirone (doses varied with range 10-60 mg/day) vs placebo	DB, MA, PG, RCT Adult outpatients with GAD HAM-A total score ≥ 18	8 trials N=509 4 weeks double-blind treatment	Primary: Hamilton Rating Scale for Anxiety (HAM-A) score, Hamilton Rating Scale for Depression (HAM-D) score, Clinical Global Impression (CGI) score to determine responders Secondary: Not reported	Primary: Overall, patients treated with buspirone demonstrated significant ($P \leq 0.001$) improvement over baseline in total HAM-A scores compared to placebo. Significantly more buspirone-treated patients (54%) were classified as responders than placebo-treated patients (28%) ($P \leq 0.001$). Patients with GAD and concurrent depressive symptoms exhibited significantly greater improvement with buspirone compared to placebo ($P \leq 0.01$ to $P \leq 0.03$ depending upon the parameter measured and severity of depressive symptoms). Weekly ratings indicated that buspirone produced a progressively increasing anxiolytic response relative to placebo throughout the 4-week double-blind treatment period in patients with GAD and coexisting depressive symptoms ($P < 0.05$ at week 1 for HAM-D and $P < 0.05$ at week 2 for HAM-A). Secondary: Not reported
Chessick et al ¹⁴ Azapirones (buspirone: 29 trials, gepirone*: 2 trials, ipsapirone*: 4 trials, lesopitron*: 1 trial) vs	MA, PG, PRO, RCT Outpatients diagnosed with GAD	36 trials N=5,908 4-14 weeks	Primary: Efficacy (HAM-A, CGI), acceptability (drop out rates, specific side effects) Secondary: Not reported	Primary: Overall, azapirones were more effective than placebo in treating GAD. Using the CGI scale in trials lasting 6 weeks, the calculated number needed to treat (NNT) for azapirones was 4.4 (95% CI: 2.16 to 15.4). Using the HAM-A assessment, lorazepam (N=40, WMD: 1.1; 95% CI: 0.29 to 1.91, $P=0.008$) and alprazolam (N=39, WMD: 1.1; 95% CI: 0.28 to 1.92, $P=0.009$) were more effective than buspirone, but diazepam was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>benzodiazepines (26 trials), hydroxyzine (1 trial), kava kava (1 trial), placebo (22 trials), venlafaxine XR (1 trial) or psychotherapy (1 trial)</p> <p>Trials may have had more than 2 arms.</p>				<p>comparable in efficacy to buspirone (N=19, WMD: -0.20; 95% CI: -7.45 to 7.05, $P=0.96$). Another small study (N=51) reported comparable efficacy between buspirone and diazepam in treating GAD, but buspirone did not show equal efficacy until 6 weeks demonstrating a more rapid improvement on diazepam (P values not reported).</p> <p>Utilizing the CGI scale, buspirone was comparable in efficacy to venlafaxine XR 75 mg (N=182, RR: 0.74; 95% CI: 0.41 to 1.34) and venlafaxine XR 150 mg (N=184, RR: 1.24; 95% CI: 0.69 to 2.21) ($P=0.47$); but, venlafaxine XR 150 mg appeared to be more effective than venlafaxine XR 75 mg (no P value reported).</p> <p>The meta-analysis was not able to conclude if buspirone was more effective than kava kava ($P=0.3$) or psychotherapy (P value not reported).</p> <p>Significantly fewer participants dropped out who were on buspirone compared to placebo (RR: 0.68; 95% CI: 0.49 to 0.94, $P=0.02$).</p> <p>Significantly fewer participants dropped out on benzodiazepines compared to buspirone (RR: 1.24; 95% CI: 1.01 to 1.52, $P=0.04$).</p> <p>There was no difference in drop out rates between buspirone and venlafaxine XR 75 mg ($P=0.92$) or 150 mg ($P=0.12$), and kava kava ($P=0.48$).</p> <p>None of the studies reported significant side effects. Overall, side effects were more common in the drug treated groups than in the placebo treated groups. Patients on buspirone reported more dizziness ($P=0.00005$) and nausea ($P=0.02$) compared to those on placebo.</p> <p>Patients receiving buspirone reported less drowsiness ($P<0.00001$), fatigue ($P=0.00001$), nervousness ($P=0.0006$), depression ($P<0.00001$), insomnia ($P=0.01$) and sleep problems ($P=0.02$) compared to benzodiazepines, while</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>those on benzodiazepines reported less nausea ($P=0.03$) and dizziness ($P=0.02$) compared to buspirone. In the trial that discontinued either diazepam or buspirone at either 6 or 12 weeks, neither group had worsening symptoms of anxiety, but those on diazepam did show withdrawal symptoms at 6 weeks compared to those on buspirone ($P<0.001$). In the one extension trial with a taper off, 25% of patients on ipsapirone showed rebound anxiety symptoms compared to 40% of patients on lorazepam ($P<0.001$).</p> <p>Patients on buspirone reported less dry mouth ($P=0.03$) compared to venlafaxine XR while those on venlafaxine XR reported less dizziness ($P<0.00001$) compared to buspirone. No differences in side effects were reported between buspirone and kava kava ($P=0.5$).</p> <p>Secondary: Not reported</p>
Mitte et al ¹⁵ Benzodiazepines (mostly diazepam, alprazolam, lorazepam) vs azapirones (mostly buspirone) vs placebo	MA Patients with GAD	48 trials N=12,053 Not reported (minimum duration for inclusion was 14 days)	Primary: Anxiety (HAM-A, HAM-D), clinical significance Secondary: Not reported	Primary: Pharmacotherapy showed better results compared to placebo in reducing both anxiety and depression symptoms. There were no significant differences in efficacy, in terms of anxiety and depression, between the benzodiazepines and azapirones (P value not reported). Significantly fewer patients in the benzodiazepine group dropped out of the study (20.5% vs 30.7%, $P<0.05$). Secondary: Not reported
Blanco et al ¹⁶ Benzodiazepines	MA Patients being	23 trials N=2,954	Primary: Outcome data on the Liebowitz Social	Primary: In terms of LSAS, effect sizes of each medication group were: clonazepam (0.97), gabapentin (0.78), phenelzine (0.66), brofaromine (0.66), SSRIs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(clonazepam, bromazepam*, alprazolam) or antidepressants (SSRI [fluvoxamine, paroxetine, sertraline], MAOI [phenelzine], reversible inhibitor of monoamine-oxidase-A [RIMA; moclobemide*, brofaromine*]) or β -blockers (atenolol) or gabapentin or buspirone vs placebo	treated for social anxiety disorder	Duration varied (6-20 weeks)	Anxiety Scale (LSAS) or a categorical measure of status Secondary: Proportion of responders with CGI score change of 1 or 2 (eg, "very much" or "much improved," respectively)	(0.65), moclobemide (0.25), atenolol (0.10), and buspirone (0.02). No statistical differences were detected between these medications or medication groups. Secondary: In terms of responders, effect sizes of each medication group were: benzodiazepines (16.61), brofaromine (6.96), phenelzine (4.10), gabapentin (3.78), SSRIs (3.22), atenolol (1.36), and moclobemide (1.27). No statistical differences were detected between these medications or medication groups.
Lader et al ¹⁷ Buspirone 20 mg/day (5 mg in AM and midday, 10 mg in	DB, MC, PC, PG, RCT Adult outpatients	N=244 6 weeks	Primary: HAM-A scores Secondary:	Primary: Hydroxyzine ($P<0.02$) but not buspirone ($P=NS$) significantly improved HAM-A scores over placebo after 28 days of treatment. HAM-A scores were not significantly different between hydroxyzine and buspirone (P

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
PM) vs hydroxyzine (salt not specified) 50 mg/day (12.5 mg in AM and midday, 25 mg in PM) vs placebo	with GAD HAM-A total score ≥ 20		CGI, Montgomery-Asberg Depression Rating Scale (MADRS), Hospital Anxiety and Depression (HAD) Scale, Echelle Dyscontrol Comportementale (EDC), Ferreri Anxiety Rating Diagram (FARD), Tyrer Withdrawal Symptom Scale	value not reported). Secondary: Significantly ($P < 0.02$) more patients on hydroxyzine improved CGI scores than placebo. There was no significant difference between buspirone and placebo (P values not reported). With respect to the MADRS, both buspirone and hydroxyzine patients were significantly better than placebo ($P < 0.001$). HAD scores for both depression ($P < 0.01$ for buspirone, $P < 0.02$ for hydroxyzine) and anxiety ($P < 0.001$ for both buspirone and hydroxyzine) were significantly better with the active drugs compared to placebo. The EDC ($P < 0.02$ for both buspirone and hydroxyzine) and FARD total scores ($P < 0.001$ for both buspirone and hydroxyzine) were also significantly better than placebo. There was no rebound with respect to HAM-A or other efficacy variables following placebo substitution at day 28. Both the buspirone and hydroxyzine patients continued to improve. No significant withdrawal symptoms for either active drug were detected on the Tyrer Scale. Both active treatments were very well tolerated. The only side effects affecting more than 5% of the exposed patients were headache and migraine (6.1%) in the buspirone-treated patients (0% in hydroxyzine and 2.5% in placebo patients) and somnolence in the hydroxyzine group (9.9%) as compared with 4.9% in the buspirone and none in the placebo group.
Llorca et al ¹⁸ Hydroxyzine (salt not specified) 50 mg/day (12.5 mg in AM and noon, 25 mg	DB, MC, PG, RCT Adult outpatients with GAD	N=334 18 weeks	Primary: HAM-A scores Secondary: Responder and	Primary: Mean change in HAM-A scores from baseline was significantly greater for hydroxyzine (-12.16) compared with placebo (-9.64, $P = 0.019$). Bromazepam was also significantly more effective than placebo in decreasing HAM-A scores ($P \leq 0.03$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
PM) or bromazepam* 6 mg/day (1.5 mg in AM and noon, 3 mg in PM) vs placebo	HAM-A total score ≥ 20		remission rates, change in Clinical Global Impressions-Severity (CGI-S) scale score and HAD scale score, maintenance of treatment efficacy, evaluation of rebound and withdrawal symptoms, safety	<p>Secondary: Results at endpoint for percentage of responders ($P=0.003$), remission rates ($P=0.028$), change in CGI-S scale score ($P=0.001$), HAD scale score ($P=0.008$), and maintenance of efficacy ($P=0.022$) on day 84 also confirmed the efficacy of hydroxyzine over placebo.</p> <p>The study showed no statistically significant difference between hydroxyzine and bromazepam; however, the study was not designed or powered to detect differences between these 2 active treatments.</p> <p>Efficacy was significantly maintained vs placebo in 86.5% of patients in the hydroxyzine group ($P=0.022$) and in 88.1% of patients in the bromazepam group ($P=0.010$) until day 84.</p> <p>In the placebo, hydroxyzine, and bromazepam groups, only 10.1%, 14.7% and 14.0% of patients, respectively, experienced at least 1 adverse event considered to be related to treatment. Safety results were comparable in the 3 groups with the exception of drowsiness, which was reported most frequently in the bromazepam group (7.9%), followed by hydroxyzine (3.9%) and then placebo (1.8%) (P values not reported).</p> <p>There were no statistically significant differences between each treatment group with regards to rebound effect (P values not reported). Differences in withdrawal symptoms that reached statistical significance were the following: hydroxyzine induced more sweating than placebo ($P=0.048$) and bromazepam induced more sleep disturbances than placebo ($P=0.002$).</p>

*Not available in the United States

Drug regimen abbreviations: AM=morning, MAOI=monoamine oxidase inhibitor, PM=evening, SSRI=selective serotonin-reuptake inhibitor, XR=extended-release

Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NNT=numbers needed to treat, PC=placebo-controlled, PG=parallel-group, PRO=prospective,

RCT=randomized controlled trial, WMD=weighted mean difference

Miscellaneous abbreviations: CGI=Clinical Global Impression, CGI-S=Clinical Global Impressions-Severity, EDC=Echelle Dyscontrole Comportementale, FARD=Ferreri Anxiety Rating Diagram,

GAD=generalized anxiety disorder, HAD=Hospital Anxiety and Depression, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, LSAS=Liebowitz Social Anxiety Scale,

MADRS=Montgomery-Asberg Depression Rating Scale

Tolerance

There are limited studies that have evaluated the long-term safety and efficacy of these agents.

Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence.¹⁶

IX. Conclusions

The non-benzodiazepine anxiolytic medications are primarily used for the treatment of anxiety disorders. Currently, none of these agents are considered to be first-line for any of the anxiety disorders, primarily due to questions of their tolerability and safety. In addition, these guidelines recognize that more clinical evidence supports the use of SSRI antidepressants in anxiety states and that SSRI medications are generally better tolerated.

Direct comparison trials of the agents within this class are limited and there is insufficient evidence that demonstrates that any agent in the class is safer or more effective than another. Buspirone, hydroxyzine hydrochloride and pamoate and meprobamate are available in at least one generic dosage form or strength.

X. Recommendations

In recognition of the role of buspirone, hydroxyzine hydrochloride, hydroxyzine pamoate and meprobamate in the treatment of anxiety disorders and the fact that all of these agents have an equivalent generic available today, it is recommended that:

- 1) All generic options be made available without restriction
- 2) All branded options where a generic exists require prior authorization. Criteria for approval to include documented intolerance to the generic product.

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